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First Author: Olachi Mezu-Ndubuisi
University of Wisconsin, Madison
Pediatrics
H4-431, CSC Madison, WI 53792
United States
Phone: 4109057090
olachimezu@pediatrics.wisc.edu

First Author is a: Investigator
First Author is a member of: American Society for Investigative Pathology, The American Physiological Society
First Author Degree: MD, DO, MBBS, or equivalent, O.D

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Sponsor: Olachi Mezu-Ndubuisi
Sponsor Phone: 4109057090
olachimezu@pediatrics.wisc.edu
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Aberrant Retinal Angiogenesis, Structure, and Synaptic Morphology in an *in vivo* Mouse Model of ROP

Olachi Joy Mezu-Ndubuisi[1,2], Erica Macke[3], Raja Kalavacherla[1], Amanda Nwaba[4], Akhiro Ikeda[3]. [1]Pediatrics, [2]Ophthalmology and Visual Sciences, [3]Medical Genetics, University of Wisconsin, Madison, Madison, WI, [4]Medicine, Health and Society, Vanderbilt University, Nashville, WI

Objective: Retinopathy of prematurity (ROP) is a condition of aberrant retinal vascularization in premature infants. Vascular endothelial growth factor (VEGF) is a major angiogenic factor in both physiologic and pathologic retinal angiogenesis including ROP. However, cellular changes that take place in ROP are not fully understood. The aim of this study is to understand changes in retinal morphology, vasculature, and structure in mice with oxygen-induced retinopathy (OIR), a model for ROP.

Methods: Twenty-two mice underwent hyperoxia exposure at 77% to induce OIR, while twenty-three age-matched control mice were raised in room air (RA). After anesthesia, pupils were dilated and fluorescein was injected intraperitoneally. After *in vivo* imaging at P19, P24, P32, and P47, eyes were isolated and fixed in Bouin's fixative for morphological analysis by H&E staining, and paraformaldehyde for immunohistochemistry. For immunohistochemistry, markers for photoreceptor presynapses (PSD95), bipolar cells (PKCalpha), microglia (iba1), and vascularization (VEGF) were used to investigate synaptic abnormalities, inflammation, and vascularization. To detect apoptosis, ApopTag Fluorescein In Situ Apoptosis Detection Kit (Millipore) was used.

Results: OIR mice had a vascular-avascular retinal phenotype, with more dilated veins and more tortuous arteries than RA mice in early ages. The OIR retinas showed disorganized synaptic interactions between photoreceptor cells and bipolar cells, with significant thinning in the ganglion cell, inner nuclear, inner plexiform, and outer plexiform layers. Retinal cross-sections showed altered structure in OIR mice, with dilated blood vessels and neovascularization in the inner retina. There was significantly increased microglia activity in ganglion cell, inner nuclear, and inner plexiform layers. There was increased apoptosis in OIR mice, which decreased over time, but persisted until P47. There was increased VEGF expression in bipolar cells. TUNEL staining showed increased apoptosis in OIR mice than RA mice at P19 ($P<0.001$), P24 ($P<0.001$), P32 ($P<0.001$), and P47 ($P<0.001$). Apoptosis decreased over time with developmental maturity of the OIR mice, but persisted at P47.

Conclusion: Our results demonstrate patchy vascular–avascular phenotype, defective synaptic interactions and persistent apoptosis in the OIR retina, which affected retinal vascularization, and structure in the long term. Our study aids the understanding of the cellular and molecular complexities of the retina following oxidative stress, and could lead to potential new therapeutic targets.